

Optimizing Economic Outcomes in Acute Exacerbations of Chronic Bronchitis

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The treatment of community-acquired respiratory tract infections, such as acute exacerbations of chronic bronchitis (AECB), constitutes a huge socioeconomic burden. In most cases, an antimicrobial agent is advocated to lessen morbidity and prevent serious clinical sequelae. Use of antimicrobial agents for AECB, however, is controversial, as it is difficult to distinguish between bacterial and nonbacterial AECB, and only marginal benefits have been reported. Antimicrobial agents, however, have reduced relapse rates, prolonged the time between exacerbations, shortened the duration of symptoms, and reduced the need for hospitalization. Microbiologic resistance and individual patient characteristics play important roles in determining the most appropriate antimicrobial agent for patients with AECB. More research on the effect of resistant bacteria on antimicrobial response rates will enable physicians to prescribe economically rational antimicrobial therapy for this common infection.

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The treatment of community-acquired respiratory tract infections (RTIs), such as acute exacerbations of chronic bronchitis (AECB), constitutes a huge socioeconomic burden. In most instances, use of an appropriate antibiotic is advocated to lessen morbidity and prevent serious clinical sequelae. Use of antibiotics for AECB is controversial, however, due to the difficulty of distinguishing between bacterial and nonbacterial AECB and the marginal benefits of antibiotics reported in early studies. Cost is another factor. However, it is necessary to look beyond the initial antibiotic cost to the larger overall management costs when evaluating the economic rationale for antibiotic use in AECB. Indeed, antibiotic treatment is associated with lower relapse rates, longer periods between exacerbations, shorter duration of symptoms, and reduced hospitalizations.

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Community-acquired RTIs are among the most prevalent of infectious diseases and represent a considerable global burden. Lower RTIs, including AECB and pneumonia, represent a serious clinical challenge, particularly in the face of increasing global antimicrobial resistance. They account for nearly half of all community-acquired infections and are the leading cause of death from infectious diseases in the United States.¹ Worldwide, lower RTIs were responsible for 4.3 million deaths in 1990.² Several strategies show promise for optimizing the clinical and economic outcomes associated with lower RTIs, particularly AECB.

The Significant Socioeconomic Burden of AECB

The term AECB has no precise definition but is typically bacterial in origin. It presents as a worsening of symptoms associated with the persistent inflammation and irritation of the bronchial tree that occurs in chronic bronchitis. Characteristic symptoms of AECB include change in sputum color, consistency, or amount, accompanied by an increase in cough, dyspnea,

Table 1. Common Etiologies of AECB⁶

Bacteria	Atypical Pathogens	Viruses
Nontypeable <i>Haemophilus influenzae</i>	<i>Mycoplasma pneumoniae</i>	Rhinoviruses
<i>Moraxella catarrhalis</i>	<i>Chlamydia pneumoniae</i>	Influenzae A and B viruses
<i>Streptococcus pneumoniae</i>		Parainfluenzae
<i>Haemophilus parainfluenzae</i>		Coronavirus
<i>Pseudomonas aeruginosa</i>		Herpes simplex virus
<i>Staphylococcus aureus</i>		Respiratory syncytial virus
Opportunistic gram-negative organisms		Adenovirus

AECB = acute exacerbations of chronic bronchitis.

and chest tightness. Exacerbations occur more commonly in smokers and in patients aged 45 years and older. If left untreated, AECB can result in inflammatory damage, which may contribute further to the progressive deterioration in respiratory function associated with chronic bronchitis. Antibiotic treatment therefore is initiated with the objective of limiting this progression, providing relief from symptoms, and reducing disability.

As well as causing significant morbidity, AECB is also associated with high socioeconomic cost. In the U.S. alone, for example, over 14 million cases of chronic bronchitis are reported annually, with each patient experiencing an average of one acute exacerbation/year. Chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the U.S.,³ frequently develops alongside chronic bronchitis and accounts for 14 million office visits and 500,000 hospitalizations/year.⁴ Annual costs associated with treatment of AECB exceed \$2 billion.⁵

Evolving Etiology and Implications for Antibiotic Selection

Table 1 shows the pathogens most commonly implicated in AECB.⁶ The most frequent bacterial causes are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*,⁶ which together account for approximately 70% of all episodes of AECB.⁷ In recent years, so-called atypical respiratory pathogens, such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, have emerged as important pathogens in AECB; these pathogens are thought to precipitate up to 10% of exacerbations.⁸ Up to 30% of AECB episodes are thought to be viral in etiology, the most common viral cause being the rhinovirus.⁷

In most cases, the microbial etiology of a particular AECB episode is not identified at the time of treatment and antibiotics therefore are

administered empirically, at least in the initial phase of treatment. This approach requires agents that have a spectrum of activity encompassing each of the key bacterial pathogens likely to be encountered. Traditionally, amoxicillin (or ampicillin), sulfamethoxazole-trimethoprim (SMX-TMP), tetracyclines, and erythromycin have been considered first-line agents for treatment of AECB. However, the clinical utility of these agents is likely to be hampered by the increasing global spread of drug-resistant pathogens. Indeed, β -lactamase production in up to 40% of *H. influenzae* and more than 90% of *M. catarrhalis* isolates renders these strains resistant to penicillins and cephalosporins.^{9, 10} Furthermore, resistance to penicillin and macrolides has spread at an alarming rate through *S. pneumoniae*.⁹

The increasing resistance to existing antibiotics among key respiratory pathogens is one of the factors driving the search for novel classes of antimicrobials. New options for treating AECB include the cephalosporins, second-generation macrolides, and newer fluoroquinolones with enhanced antipneumococcal activity. In addition, the ketolides are a new class of antibiotics designed specifically to combat community-acquired RTIs, particularly those caused by resistant organisms. Telithromycin (HMR 3647) is the first member of this class to reach clinical development. Numerous in vitro studies confirm the potent activity of telithromycin against pathogens commonly implicated in community-acquired RTIs, irrespective of their β -lactam or macrolide susceptibility.

The Role of Antibiotics in the Treatment of AECB

The use of antibiotics in the treatment of AECB has been under considerable debate since the early 1970s. Arguments against the routine prescribing of antibiotics for AECB include the

difficulties in distinguishing between AECB of bacterial and nonbacterial etiology and the marginal benefits reported from antibiotic interventions. Some placebo-controlled trials showed no benefit with antibiotic therapy. It also has been suggested that such intervention might delay diagnosis of serious underlying disease. In addition, the cost of antibiotics (particularly of the newer agents) has been used as justification for frugal prescribing in some instances. However, when evaluating the economic rationale for antibiotic use in AECB, it is necessary to look beyond the initial antibiotic acquisition cost to the larger overall costs of managing AECB, including physician visits, hospitalizations, and lost productivity due to work absenteeism.

A landmark study published in 1987 provided the first definitive evidence of the place of antibiotics in the treatment of AECB.¹¹ In this study, 173 patients with AECB and COPD were randomized to receive either antibiotic therapy or placebo. Patients who experienced subsequent exacerbations were crossed over to the other arm of the study. The antibiotics used in this trial were SMX-TMP, amoxicillin, and doxycycline in standard dosages. Patients were stratified by severity of exacerbation, based on subjective criteria. Overall, the study demonstrated that the success rate for antibiotic-treated exacerbations was 1.24 times higher than for the placebo-treated arm (68% vs 55%). Of importance from an outcome standpoint, 34% of placebo-treated patients deteriorated, compared with 18% in the antibiotic-treated arm. This difference was most marked for patients with the severest disease, where deterioration was more than 2-fold greater in the placebo arm compared with the antibiotic arm. In relation to previously published AECB trial results,¹²⁻¹⁸ the authors identified a number of consequences of not treating AECB episodes with antibiotics. These included a higher failure rate (and thus shorter periods between acute infections), longer duration of symptoms, and theoretically increased hospital admissions.

The rationale for using antibiotics for AECB is further supported by studies showing that vaccination against *H. influenzae* reduces the number of AECB episodes.¹⁹ Furthermore, in selected patient groups, prophylactic use of antibiotics has been found to reduce AECB and accelerate recovery by slowing the deterioration of respiratory status.²⁰ Finally, a meta-analysis of nine randomized, placebo-controlled trials demonstrated a small but statistically significant

clinical benefit of using antibiotics in the treatment of AECB.²¹

Clinical and Economic Considerations

A number of factors affect the clinical and economic outcomes of antibiotic therapy for AECB, including patient profiles, choice of antibiotic, and local resistance patterns. However, studies of antibiotic therapy for AECB have failed to either account for differences among patients or examine the effect of increasing rates of antimicrobial resistance on clinical and economic outcomes. To determine whether the antibiotic prescribed by the pulmonologist affected the relative efficacy and costs of treating AECB, a retrospective review of patients with COPD and AECB was performed. The medical records of patients with these conditions who visited the Pulmonary Department of the Creighton University School of Medicine over a 4-year period were studied.²² Chronic bronchitis was defined as meeting two or more of the following criteria: increased cough and sputum production, change in color or tenacity of sputum, decreased breath sounds or increased wheezing, increased dyspnea, and fever above 100.4°F (in patients not receiving oral steroids). The chosen antibiotic, length of therapy, antibiotic failure or hospitalization (within 2 weeks of initial therapy), length of time between AECB episodes, and costs (antibiotic costs and total costs of AECB treatment) were recorded. Based on the opinion of pulmonologists, antibiotics were categorized as first line (amoxicillin, SMX-TMP, tetracycline, erythromycin), second line (cephradine, cefuroxime, cefaclor, cefprozil), and third line (amoxicillin-clavulanate, azithromycin, ciprofloxacin). Of the 285 patient medical records reviewed, 60 patients met the eligibility criteria and were included in the analysis. This included 224 AECB episodes requiring antibiotic treatment, with an average of 3.7 episodes/patient. Of these AECB episodes, 100 were treated with first-line agents (predominantly amoxicillin and SMX-TMP), 67 with second-line agents (predominantly cefaclor and cefuroxime), and 57 with third-line antibiotics. Ninety-five percent of patients received a first-line antibiotic at their first office visit; 48% received a second- or third-line antibiotic at their second office visit; and 23% of patients who received second-line antibiotics also received a third-line agent at a third office visit. In 34 of the 224 episodes (15.2%), therapy failed

Table 2. Mean Clinical and Economic Outcomes for 60 Patients with COPD Treated with Either First-, Second-, or Third-Line Antibiotics for AECB²²

	First-line (n=100)	Second-line (n=67)	Third-line (n=57)
Duration of antibiotic therapy (days) ^a	8.9	8.3	7.5
Time between AECB episodes (wks) ^b	17.1	22.7	34.3
Pharmacy cost (\$) ^c	10.30	24.45	45.40
Total cost of AECB (\$) ^d	942	563	542

AECB = acute exacerbations of chronic bronchitis.

^ap<0.02.

^bp<0.005.

^cp=0.0001 (one-way analysis of variance).

^dIncludes office charges, radiology charges, antibiotic costs, and hospitalization charges.

within 2 weeks. Both treatment failure and hospitalizations were significantly more frequent in patients receiving first-line antibiotics than in those receiving third-line therapy (Figure 1). Although the pharmacy costs for treating each AECB episode were lower with first-line agents, there was a trend toward lower total cost for managing patients with second- and third-line agents (Table 2).²² It was concluded that this study found that in patients with COPD experiencing an AECB, the use of third-line antibiotics significantly reduced treatment failure rates and the need for hospitalization, while prolonging the time between AECB episodes.

This study is the first to show the effect of antibiotic selection on both clinical and economic outcomes in AECB. Its findings are

supported by a recent study demonstrating that administration of antibiotics significantly reduced relapse rates in outpatients with acute exacerbations of COPD.²³ Furthermore, of the patients treated with antibiotics, relapse was highest among those who had received amoxicillin. Further prospective studies are warranted to help identify which patients would benefit most from the more expensive antibiotics, thus helping to reduce the total cost of managing patients with AECB episodes.

Patient Classification

A 1997 review of the treatment of AECB presented evidence that treatment outcome might reflect a number of patient-specific variables, in

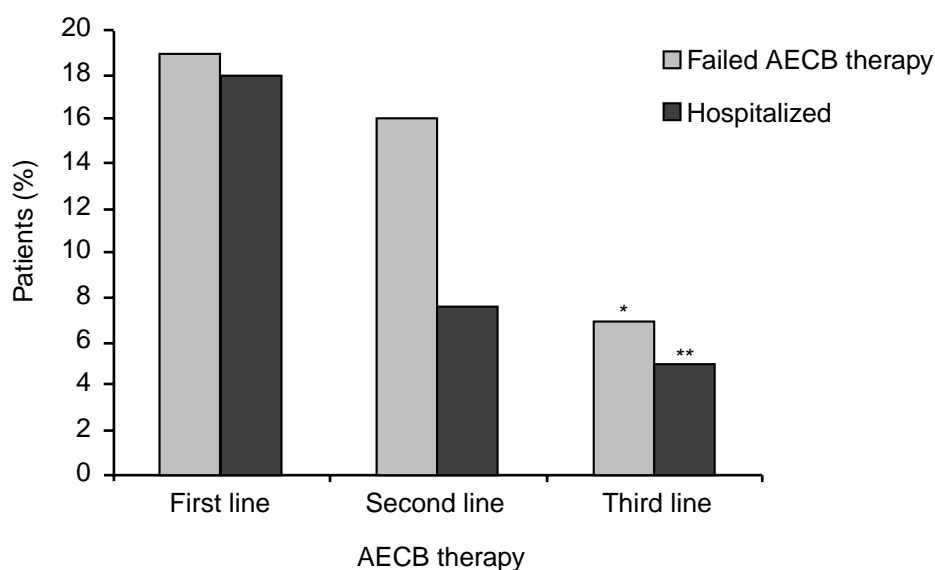


Figure 1. Percentage of patients with acute exacerbations of AECB failing therapy or requiring hospitalization within 2 weeks of completing a course of first-, second-, or third-line antibiotic therapy.²² AECB = acute exacerbations of chronic bronchitis. *p<0.05; **p<0.02.

particular the presence of cardiopulmonary disease, such as heart failure, and the number of exacerbations/year.²⁴ Indeed, patients with four or more exacerbations/year may be at risk of antibiotic failure and may require a third-line antibiotic (e.g., azithromycin, amoxicillin-clavulanate, or ciprofloxacin).^{25, 26} A number of other risk factors also were identified that place a patient at increased risk of hospitalization during an acute exacerbation. These include age of 65 years or older, compromised lung function, and severe pulmonary and nonpulmonary dysfunction. However, no studies to date have documented whether the risk of hospitalization might be linked to the prevalence of resistant pathogens. These data need to be determined, as they will have a major impact on the utility of prescribing more potent antibiotics for patients at risk, such as the elderly and those with severe lung dysfunction.

Long-term Outcomes

The effect of antibiotics on long-term outcomes in AECB has been studied. A double-blind, randomized trial—the Gemifloxacin Long-term Outcome in Bronchitis Evaluation (GLOBE) study—compared gemifloxacin (an investigational quinolone) with clarithromycin in patients with AECB for 26 weeks.²⁷ Over this period, patients who received gemifloxacin had significantly fewer AECB relapses compared with those receiving clarithromycin (71% success compared with 59%, $p < 0.02$). Moreover, hospitalization was required for only 5 of 214 (2.3%) patients receiving gemifloxacin, compared with 14 of 224 (6.3%) patients who received clarithromycin ($p = 0.059$).

Another research group determined antibiotic treatment intervals in a community-based program.²⁸ In this study, patients with AECB were categorized according to their antibiotic therapy: β -lactams (185 patients), macrolides (180), and quinolones (131). Overall, the mean time interval between antibiotic courses for patients experiencing an AECB relapse (as determined by the prescribing physician) was significantly longer for patients treated with quinolones (27.5 days, $p = 0.03$) than for those treated with either macrolides or β -lactams (17.5 and 18 days, respectively).

Conclusion

Regular reevaluation of antibiotic treatment approaches for AECB is warranted, with the aim

of minimizing treatment failures and subsequent hospitalizations, thereby reducing costs, while containing the spread of antimicrobial resistance. Guidelines for treatment of AECB are still evolving. Nevertheless, it is clear that clinical risk stratification (taking into account disease severity and comorbidity) and studies of health outcomes are helping to provide the necessary rationale for clinically and economically effective use of antimicrobials for AECB. The infection-free interval might be an appropriate outcome measure with which to compare differences between antibiotics in patients with AECB.²⁹ In addition, resistant organisms should be cultured from patients with AECB to determine whether resistance is a factor in the outcome of AECB.

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